REMARKS

A check for $905 for the fee for filing of a Request for Continued Examination ($395) and the fee for a three-month extension of time ($)510 accompanies this response. Any fees that may be due in connection with this application throughout its pendency may be charged to Deposit Account No. 06-1050. If a Petition for Extension of time is needed, this paper is to be considered such Petition.

Claims 1, 2, 3, 5, 10-13, 19, 20, 34-36, 40-46, 48-55, 108, 109, 113, 114, 115, 116, 118-120 and122-126 are pending. Claims 6, 7, 9, 14, 16, 18, 56, 57, 72-75, 74 , 91, 127-129 and 137 are cancelled without prejudice or disclaimer. Claims 1, 5, 12, 13, 18, 43, 74, 108 and 113 are amended. Also amended are claims 43 and 122, which are withdrawn from consideration. Claims 10, 43-46, 48-57, and 108-126 are withdrawn from consideration but are retained for possible rejoinder. Non-elected subject matter also is retained in pending examined claims for possible rejoinder. Claim 1 is amended for clarity to render it clear that the claim is directed a single chain MTSP protease domain polypeptide or catalytically active portion thereof or to a polypeptide that contains such protease domain but that does not contain any other part of that MTSP. Hence claim 1 does not read on full-length MTSPs. No new matter is added.

I. OBJECTION TO CLAIMS 11-14 AND 34 AS ALLEGEDLY DIRECTED TO NON-ELECTED SUBJECT MATTER

Claims 11-14 and 34 are objected to for allegedly being drawn to non-elected subject matter. This subject matter is retained pending a determination of the allowability of claim 1. If claim 1 is allowed, then the non-elected subject matter in these claims, which are within the scope of claim 1, will be allowable.

As discussed below, in addition to identifying new full-length MTSP polypeptides, the instant applicant has discovered that the protease domain as a single chain polypeptide that contains only the protease domain of the MTSP possesses protease activity. Absent the earlier application of Dr. Edwin Madison *et al.*, there is no art of record that teaches or suggests that a serine protease domain as a single chain containing only the protease domain and no longer portion possess protease activity. The earlier application of Dr. Edwin Madison is directed to endotheliases, not to the MTSPs of the instant application. All other art of record and of which the instant applicant is aware describes the necessity for an activation cleavage event that produces a two chain polypeptide as a requisite for proteolytic activity. Thus, as discussed below, no reference of record teaches or suggests *a substantially isolated* protease domain of an MTSP.

II. THE REJECTION OF CLAIMS UNDER 35 U.S.C. §112, SECOND PARAGRAPH

Claims 1, 2, 3, 5-7, 11-14, 16, 18-20, 34-36, 40-42 and 137 are rejected under 35 U.S.C. § 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. The bases set forth by the Examiner are discussed in turn below. This rejection is respectfully traversed.

1) Claim 1 and its Dependent Claims

Claim 1 and claims depending therefrom are rejected under 35 U.S.C. § 112, second paragraph as being indefinite, because the Examiner urges that the phrase "the MTSP portion is the only portion of the single-chain polypeptide from the MTSP" in claim 1 "appears to be redundant and only adds confusion to the claim since the preamble of the claim limits that the single-chain polypeptide comprises a MTSP portion."

Applicant respectfully disagrees. The recitation "the MTSP portion is the only portion of the single-chain polypeptide from the MTSP" specifies that the MTSP protease domain is the only MTSP portion in the polypeptide. Claim 1 is amended herein to more distinctly recite that the claimed polypeptide includes an MTSP protease domain or catalytically active portion thereof and that the MTSP protease domain or catalytically active portion thereof is the only MTSP portion in the polypeptide. Hence the claim does not read on any full-length MTSP but only on the isolated protease domain or on non-MTSP polypeptides that include the protease domain.

Claims 6-9

Claims 6-9 are rejected under 35 U.S.C. § 112, second paragraph as being indefinite, because it is alleged that it is not clear how one of skill in the art would identify the claimed characteristics. Applicant respectfully submits that claim 8 previously was cancelled in this application. In order to advance prosecution, but without acquiescing to the rejection, claims 6, 7 and 9 are cancelled herein without prejudice or disclaimer. Thus, the rejection as applied to claims 6, 7 and 9 is moot.

Claims 16 and 18

Claims 16 and 18 are rejected under 35 U.S.C. § 112, second paragraph as being indefinite because it is alleged that the metes and bounds of the phrase "substrate therefore" in the context of claims 16 and 18 are not clear. In order to advance prosecution, and without acquiescing to the rejection, these claims are cancelled herein without prejudice or disclaimer, rendering this ground for rejection moot.

III. REJECTION OF CLAIMS 1-3, 5-7, 9, 11, 16, 18-20, 34-36, 40-42 AND 137 UNDER 35 U.S.C. §112, FIRST PARAGRAPH - POSSESSION

Claims 1-3, 5-7, 9, 11, 16, 18-20, 34-36, 40-42 and 137 are rejected under 35 U.S.C. §112, first paragraph, as allegedly containing subject matter that was not described in the specification in such a way as to reasonably convey to one skilled in the art that the inventor, at the time the application was filed, had possession of the claimed subject matter. The Examiner states that the claims are directed to a genus of polypeptides that include a protease domain or catalytically active portion thereof of a type-II membrane-type serine protease (MTSP) from any source including any or all recombinants, variants and mutants of MTSP or MTSP1. The Examiner alleges that the claims thus are allegedly drawn to polypeptides having any structure and allegedly are thus a structurally diverse genus. The Examiner states that the description of solely structural features present in all members of the genus is not sufficient to be representative of the attributes and features of the entire genus. The Examiner alleges that there is insufficient written description because the specification allegedly teaches only four species, and the Examiner contends that the disclosure of four species is not enough to describe the whole genus, and alleges that there is no evidence on record of the relationship between the structure of the serine protease domains of SEQ ID NOs. 2, 4, 6 and 11 and the structure of any or all MTSP polypeptides or a catalytically active portion of an MTSP polypeptide. The rejection is respectfully traversed.

RELEVANT LAW

The purpose behind the written description requirement is to ensure that the patent applicant had possession of the claimed subject mater at the time of filing of the application. The relevant law and a discussion of the Patent Office Guidelines are set forth in the previous responses of record in this application, which are incorporated by reference herein. Briefly, the Federal Circuit has discussed the application of the written description requirement of the first paragraph of 112 to claims in the field of biotechnology. *See University of California v. Eli Lilly and Co.*, 119 F.3d 1559, 43 U.S.P.Q.2d 1398, 1406 (Fed. Cir. 1997). The court explained that:

> In claims involving chemical materials, generic formulae usually indicate with specificity what the generic claims encompass. One skilled in the art can distinguish such a formula from others and can identify many of the species that the claims encompass. Accordingly, such a formula is normally an adequate description of the claimed genus . . . a generic statement such as "vertebrate insulin or "mammalian insulin without more, is not an adequate written description of the genus because it does not

> distinguish the claimed genus from others, except by function. It does not specifically define any of the genes that fall within its definition. It does not define any structural features commonly possessed by members of the genus that distinguish them from others. One skilled in the art therefore cannot, as one can do with a fully described genus, visualize or recognize the identity of the members of the genus. A definition by function, as we have previously indicated, does not suffice to define the genus because it is only an indication of what the gene does, rather than what it is.

The court also stated that "[a]written description of an invention involving a chemical genus, like a description of a chemical species, 'requires a precise definition, such as by structure, formula, [or]chemical name,' of the claimed subject matter sufficient to distinguish it from other materials." *Id.* at 1567, 43 U.S.P.Q.2d at 1405. Finally, the court addressed the manner by which a genus of might be described. "A description of a genus of may be achieved by means of a recitation of a representative number of defined by nucleotide sequence, falling within the scope of the genus or of a recitation of structural features common to the members of the genus, which features constitute a substantial portion of the genus." *Id.*

The Federal Circuit also has addressed the written description requirement in the context of biotechnology-related subject matter in *Enzo Biochem. Inc. v. Gen-Probe*, 296 F.3d 1316, 63 USPQ2d (BNA) 1609 (Fed. Cir. 2002). The *Enzo* court adopted the standard that:

> the written description requirement can be met by 'showing that an invention is complete by disclosure of sufficiently detailed, relevant identifying characteristics . . . complete or partial structure, other physical chemical properties, functional characteristics when coupled with a known or disclosed correlation between function and structure, or some combination of such characteristics.'

The court in *Enzo* adopted its standard from the Written Description Examination Guidelines. The Guidelines apply to proteins as well as nucleic acid molecules.

It is well-settled that the written description requirement of 35 U. S. C. §112, first paragraph, can be satisfied without express or explicit disclosure of a later-claimed invention. *See, In re Herschler*, 591 F.2d 693, 700-01, 200 USPQ 711, 717 (CCPA 1979):

> "The claimed subject matter need not be described *in haec verba* to satisfy the description requirement. It is not necessary that the application describe the claim limitations exactly, but only so clearly that one having ordinary skill in the pertinent art would recognize from the disclosure that appellants invented processes including those limitations." (citations omitted).

See also Purdue Pharma L. P. v. Faulding, Inc., 230 F.3d 1320, 56 USPQ2d 1481 (Fed. Cir. 2000). In order to satisfy the written description requirement, the disclosure as originally filed does not have to provide *in haec verba* support for the claimed subject matter at issue.

THE CLAIMS

Claim 1 is directed to a substantially purified single-chain polypeptide that includes a protease domain of a type-II membrane-type serine protease (MTSP) or a catalytically active fragment thereof, where the MTSP protease domain or catalytically active fragment thereof is the only portion of the single-chain polypeptide from the MTSP and the MTSP protease domain or catalytically active fragment thereof has serine protease activity as a single chain. Claim 3, 5, 11, 16, 18-20, 34-36, 40-42 and 137 ultimately depend from claim 1 and are directed to various embodiments thereof.

ANALYSIS

The analysis and arguments set forth in the previous responses of record are incorporated by reference herein. In setting forth the rejection, the Examiner urges that the specification does not set forth what specific structural or physical features define the claimed polypeptides and argues that one skilled in the art could not predict the structure and function of he claimed polypeptides that include a protease domains or catalytically active portion thereof or any or all MTSP polypeptide. The Examiner alleges that the genus of claim 1 and its dependent claims are structurally diverse because it encompasses any catalytically active protease domains of any or all MTSP or all MTSP1 and has serine protease activity. The Examiner states that the claims are drawn to polypeptides having any structure and are thus drawn to a genus encompassing species having substantial variation (Office Action, page 8) and that description of solely structural features present in all members of the genus is not sufficient to be representative of the attributes and features of the entire genus (see Office Action, page 9). It respectfully is submitted that this is not correct.

It is respectfully submitted that the instant application adequately describes the claimed polypeptides to demonstrate possession of the claimed subject matter at the time of the effective filing date of each claim. As is discussed in more detail below, to satisfy the written description requirement, one need not provide an example of every species encompassed by a claim. It is sufficient to provide identifying characteristics, including structural and physical characteristics, functional characteristics coupled with known or disclosed correlation with structural characteristics to demonstrate that the applicant was in

possession of the claimed subject matter. MPEP § 2163; *see University of California v. Eli Lilly*, 119 F. 3d 1559, 1568, 43 USPQ2d 1398, 1406 (Fed. Cir. 1997). Further, the standard is an objective one, based on what one of skill in the art would recognize in the disclosure. *In re Gosteli*, 872 F.2d at 1012.

First, the structural feature, a single chain protease domain, is present in all members of the genus and is the defining and requisite property thereof. The specification clearly describes this feature and demonstrates possession thereof.

Second, as discussed above, the instant application discloses that the isolated protease domains of members of the type II transmembrane protease (MTSP) family possess protease activity as a single-chain polypeptide. The application notes and describes known MTSP and identifies the protease domains thereof. In addition, the application identifies and provides heretofore unknown MTSPs and provide full-length proteases and also the isolated protease domains. Hence application exemplifies and describes **MTSP1** (or matriptase), **MTSP3, MTSP4** and **MTSP6**, **corin** (accession nos. AF133845 and AB013874; see, Yan et al. (1999) J. Biol. Chem. 274:14926-14938; Tomia et al. (1998) J. Biochem. 124:784-789; Uan et al. (2000) Proc. Natl. Acad. Sci. U.S.A. 97:8525-8529; SEQ ID Nos. 61 and 62 for the human protein); **enteropeptidase** (also designated enterokinase; accession no. U09860 for the human protein; see, Kitamoto et al. (1995) Biochem. 27: 4562-4568; Yahagi et al. (1996) Biochem. Biophys. Res. Commun. 219:806-812; Kitamoto et al. (1994) Proc. Natl. Acad. Sci. U.S.A. 91:7588-7592; Matsushima et al. (1994) J. Biol. Chem. 269:19976-19982; see SEQ ID Nos. 63 and 64 for the human protein); **human airway trypsin-like protease** (HAT; accession no. AB002134; see Yamaoka et al. J. Biol. Chem. 273:11894-11901; SEQ ID Nos. 65 and 66 for the human protein); **hepsin** (see, accession nos. M18930, AF030065, X70900; Leytus et al. (1988) Biochem. 27: 11895-11901; Vu et al. (1997) J. Biol. Chem. 272:31315-31320; and Farley et al. (1993) Biochem. Biophys. Acta 1173:350-352; SEQ ID Nos. 67 and 68 for the human protein); **TMPRS2** (see, Accession Nos. U75329 and AF113596; Paoloni-Giacobino et al. (1997) Genomics 44:309-320; and Jacquinet et al. (2000) FEBS Lett. 468: 93-100; SEQ ID Nos. 69 and 70 for the human protein) **TMPRSS4** (see, Accession No. NM 016425; Wallrapp et al. (2000) Cancer 60:2602-2606; SEQ ID Nos. 71 and 72 for the human protein); and **TADG-12** (also designated MTSP6, see SEQ ID Nos. 11 and 12; see International PCT application No. WO 00/52044, which claims priority to U.S. application Serial No. 09/261,416).

As described in the application, all of these are members of the MTSP family and contain a protease domain, whose locus is known or that can be readily identified as described in the application. The application states:

> The protease domains as provided herein are single-chain polypeptides, with an N-terminus (such as IV, VV, IL and II) generated at the cleavage site (generally having the consensus sequence R↓VVGG, R↓IVGG, R↓IVNG, R↓ILGG, R↓VGLL, R↓ILGG or a variation thereof; an N-terminus R↓V or R↓I, where the arrow represents the cleavage point) when the zymogen is activated. To identify the protease domain an RI should be identified, and then the following amino acids compared to the above noted motif.
>
> The protease domains generated herein, however, do not result from activation, which produces a two chain activated product, but rather are single chain polypeptides with the N-terminus include the consensus sequence ↓VVGG, ↓IVGG, ↓VGLL, ↓ILGG or ↓IVNG or other such motif at the N-terminus. As shown herein, such polypeptides, although not the result of activation and not double-chain forms, exhibit proteolytic (catalytic) activity.

Hence the specification teaches a genus of peptides and teaches that the protease domain of each can be isolated an that it has proteolytic activity. Many of these polypeptides are known polypeptides, and the locus of the protease domain was known. What was not known, however, is that the protease domain can be isolated and that it exhibits proteolytic activity as a single chain. The application clearly and unequivocally demonstrates and exemplifies such polypeptides. There should be no doubt that the applicant had possession of the genus of isolated protease domains of the MTSP family at the time of filing.

1. The specification provides identifying characteristics of MTSP polypeptides, including structural and physical characteristics of MTSP polypeptides and their protease domain and correlations between structural and functional characteristics that further demonstrate possession of the claimed polypeptides.

2. The level of knowledge with respect to the identified protease domains of MTSP polypeptides was exceptionally high as of the time of filing.

3. In light of the descriptions in the specification and the level of knowledge in the art, one of skill in the art would recognize Applicant's possession of the claimed subject matter

Therefore, Applicant had possession of the claimed single-chain protease domain polypeptides that have the identifying structural and functional characteristics of an MTSP protease domain or catalytically active portion thereof.

1. The specification provides (and the claims recite) relevant identifying characteristics of MTSP polypeptides, including structural and physical characteristics of serine proteases

An objective standard for determining whether a disclosure complies with the written description requirement is an affirmative answer to the query: "does the description clearly allow persons of skill in the art to recognize that he or she invented what is claimed?" *In re Gosteli*, 872 F.2d 1008, 1012, 10 USPQ.2d 1614, 1618 (Fed. Cir.1989). The instant specification defines a genus of polypeptides as claimed such that one of skill in the art would recognize that genus. Recognition thereof is sufficient to evidence Applicant's possession of the claimed subject matter

The polypeptides of claim 1 and claims dependent thereon recite a specific structural domain of an MTSP, the protease domain or a catalytically active portion thereof. The specification describes the structural features of the protease domain, including additional structure, such as the catalytic triad, primary specificity pocket, oxyanion hole and conserved motifs (*e.g.*, see page 19, lines 3-21). The claims also recite as an additional structural limitation that the polypeptide is a single-chain. The specification teaches, and it is known in the art, that serine proteases are expressed as an inactive single-chain zymogens that are subsequently activated by cleavage of the single chain to form a two-chain polypeptide that contains the protease domain disulfide bonded to amino acids upstream of the protease domain. What was not known in the art is that an isolated single-chain form of the protease domain exhibits proteolytic function. Hence the art does not provide isolated protease domains, but provides full-length MTSP proteases and identifies cleavage sites for activation cleavage. The instant application teaches that activation cleavage is not required, so that polypeptides that contain only the protease domain exhibit activity.

2. The identified protease domains of serine proteases were well known at the time of filing

The standard for evaluating written description is objective, based on what one of skill in the art would recognize in the disclosure. *In re Gosteli*, 872 F.2d at 1012. Hence, evaluation of written description takes into account the knowledge of one of skill in the art with regard to the particular subject matter.

The claimed polypeptides are single chain polypeptides that contain the protease domain of a type-II MTSP or catalytically active portion thereof as the only portion of the single-chain polypeptide from the MTSP. As discussed above, the instant application describes and provides the protease domains (see specification and sequence listing) of at

least a dozen MTSP protease domains, including new MTSPs, such as MTSP4, heretofore unknown.

3. One of skill in the art would recognize Applicant's possession of the claimed subject matter

To satisfy the written description requirement, the issue is not whether the specification literally lists all of the possible MTSP protease domains and variants thereof that fall within the scope of the claims, but whether one of skill in the art in view of the specification would recognize that applicant had provided a genus of single-chain polypeptides with the recited protease domain structure given the disclosure of the instant application. As noted above, the application provides at least a dozen examples, provides relevant structural and functional features that uniquely identify and specify the claimed genus of polypeptides. The specification teaches that those of skill in the art recognize common elements among MTSPs and the protease domains of MTSPs, and the specification teaches a number of conserved characteristics for the MTSPs. For example, see page 49, lines 3-15, which discloses:

> The MTSPs are a family of transmembrane serine proteases that are found in mammals and also other species that share a number of common structural features including: a proteolytic extracellular C-terminal domain; a transmembrane domain, with a hydrophobic domain near the N-terminus; a short cytoplasmic domain; and a variable length stem region containing modular domains. The proteolytic domains share sequence homology including conserved his, asp, and ser residues necessary for catalytic activity that are present in conserved motifs. The MTSPs are synthesized as zymogens, and activated to double chain forms by cleavage. It is shown herein that the single chain proteolytic domain can function *in vitro* and, hence is useful in *in vitro* assays for identifying agents that modulate the activity of members of this family. Also provided are family members designated MTSP3, MTSP4 and an MTSP6 variant.

The specification provides additional structural and functional characteristics of the various MTSPs. For example, the specification teaches that the MTSP family of proteases include a serine residue that is involved in the hydrolysis of proteins or peptides. The serine residue can be part of the catalytic triad mechanism, which includes a serine, a histidine and an aspartic acid in the catalysis, or can be part of the hydroxyl/ε-amine or hydroxyl/α-amine catalytic dyad mechanism, which involves a serine and a lysine in the catalysis (for example, see page 17, lines 24-30). Further the specification teaches, for example at page 19, lines 3-24, that:

> Exemplary MTSP proteins, with the protease domains indicated, are illustrated in Figures 1-3. Smaller portions thereof that retain protease activity are contemplated. The protease domains vary in size and constitution, including insertions and deletions in surface loops. They retain conserved structure,

including at least one of the active site triad, primary specificity pocket, oxyanion hole and/or other features of serine protease domains of proteases. Thus, for purposes herein, the protease domain is a portion of a MTSP, as defined herein, and is homologous to a domain of other MTSPs, such as corin, enteropeptidase, human airway trypsin-like protease (HAT), MTSP1, TMPRSS2, and TMPRSS4, which have been previously identified; it was not recognized, however, that an isolated single chain form of the protease domain could function proteolytically in *in vitro* assays. As with the larger class of enzymes of the chymotrypsin (S1) fold (see, e.g., Internet accessible MEROPS data base), the MTSPs protease domains share a high degree of amino acid sequence identity. The His, Asp and Ser residues necessary for activity are present in conserved motifs. The activation site, which results in the N-terminus of second chain in the two chain forms is has a conserved motif and readily can be identified (see, e.g., amino acids 801-806, SEQ ID No. 62, amino acids 406-410, SEQ ID No. 64; amino acids 186-190, SEQ ID No. 66; amino acids 161-166, SEQ ID No. 68; amino acids 255-259, SEQ ID No. 70; amino acids 190-194, SEQ ID No. 72).

The specification also directs those skilled in the art to exemplary art that describes common structural features shared by the transmembrane serine proteases (for example, see page 18, lines 1-15). Thus, the specification discloses and the art recognizes that there are common conserved elements among the protease domains of MTSPs, such as the active site triad, a primary specificity pocket and an oxyanion hole. **Furthermore, the Type II transmembrane serine proteases are a recognized genus of polypeptides.**

An adequate written description for a claimed genus only has to provide "relevant, identifying characteristics" of a representative number of species (MPEP §2163). The specification provides a number of examples of MTSP protease domains, explicitly and implicitly. As noted the specification provides at least a dozen examples of MTSPs and isolated protease domains, including MTSP1, MTSP3, MSTP4 (2 splice variants) and MTSP6. As quoted above, the disclosure on pages 9-10 recites:

Other MTSP protease domains of interest herein, particularly for use in *in vitro* drug screening proteolytic assays, include, but are not limited to: corin (accession nos. AF133845 and AB013874; see, Yan *et al.* (1999) J. Biol. Chem. 274:14926-14938; Tomia *et al.* (1998) J. Biochem. 124:784-789; Uan *et al.* (2000) Proc. Natl. Acad. Sci. U.S.A. 97:8525-8529; SEQ ID Nos. 61 and 62 for the human protein); enteropeptidase (also designated enterokinase; accession no. U09860 for the human protein; see, Kitamoto *et al.* (1995) Biochem. 27: 4562-4568; Yahagi *et al.* (1996) Biochem. Biophys. Res. Commun. 219:806-812; Kitamoto *et al.* (1994) Proc. Natl. Acad. Sci. U.S.A. 91:7588-7592; Matsushima *et al.* (1994) J. Biol. Chem. 269:19976-19982; see SEQ ID Nos. 63 and 64 for the human protein); human airway trypsin-like protease (HAT; accession no. AB002134; see Yamaoka *et al.* J. Biol. Chem. 273:11894-11901; SEQ ID Nos. 65 and 66 for the human protein); hepsin (see, accession nos. M18930, AF030065, X70900; Leytus *et al.* (1988) Biochem. 27: 11895-11901; Vu *et al.* (1997) J. Biol. Chem.

> 272:31315-31320; and Farley *et al.* (1993) Biochem. Biophys. Acta 1173:350-352; SEQ ID Nos. 67 and 68 for the human protein); TMPRS2 (see, Accession Nos. U75329 and AF113596; Paoloni-Giacobino *et al.* (1997) Genomics 44:309-320; and Jacquinet *et al.* (2000) FEBS Lett. 468: 93-100; SEQ ID Nos. 69 and 70 for the human protein) TMPRSS4 (see, Accession No. NM 016425; Wallrapp *et al.* (2000) Cancer 60:2602-2606; SEQ ID Nos. 71 and 72 for the human protein); and TADG-12 (also designated MTSP6, see SEQ ID Nos. 11 and 12; see International PCT application No. WO 00/52044, which claims priority to U.S. application Serial No. 09/261,416).

As noted in the quoted paragraph, sequences of these protease are provided. Also provided are sequences of MTSP3, the MTSPs 4, and MTSP5 (see page 52, lines 12-31):

> Specific sequences for the following human MTSPs and domains thereof are provided as follows: SEQ ID No. 3 MTSP3 nucleic acid sequence; SEQ ID No. 4 MTSP3 amino acid sequence; SEQ ID No. 5 MTSP4 nucleic acid encoding the protease domain; SEQ ID No. 6 MTSP4 amino acid sequence of the protease domain; SEQ ID No. 7 MTSP4-L nucleic acid sequence; SEQ ID No. 8 MTSP4-L amino acid sequence; SEQ ID No. 9 MTSP4-S nucleic acid sequence; SEQ ID No. 10 MTSP4-S amino acid sequence; SEQ ID No. 11 MTSP6 nucleic acid sequence; SEQ ID No. 12 MTSP6 amino acid sequence. SEQ ID No. 1 sets forth the nucleic acid sequence of the long form of MTSP1; SEQ ID No. 2 the encoded amino acid sequence; SEQ ID No. 49 sets forth the sequence of a protease domain of an MTSP1, and SEQ ID No. 50 the sequence of the encoded single chain protease domain thereof. Figures 1-3 depict the structural organization of the MTSP3, MTSP4 and MTSP6, respectively.
>
> In particular, exemplary protease domains include at least a sufficient portion of sequences of amino acids set forth as amino acids 615-855 in SEQ ID No. 2 (encoded by nucleotides 1865-2587 in SEQ ID No. 1; see also SEQ ID Nos. 49 and 50) from MTSP1 (matriptase), amino acids 205-437 of SEQ ID NO. 4 from MTSP3, SEQ ID No. 6, which sets forth the protease domain of MTSP4, and amino acids 217-443 of SEQ ID No. 11 from MTSP6.

Hence, the specification explicitly discloses at least a dozen MTSP family member proteases (matriptase, corin, enteropeptidase, human airway trypsin-like protease, hepsin, TMPRS2, TMPRSS4 and TADG-12) and provides specific nucleic acid sequences and amino acid sequences for exemplary species.

The specification states that the claimed single-chain polypeptide includes an MTSP protease domain or catalytically active portion thereof that can be from any MTSP family, for example from a mammal, including human MTSP. For example, see page 8, line 30 through page 9, line 8, which recites:

> The protease domains provided herein include, but are not limited to, the single chain region having an N-terminus at the cleavage site for activation of the zymogen, through the C-terminus, or C-terminal truncated portions thereof that exhibit proteolytic activity as a single-chain polypeptide in *in vitro* proteolysis

> assays, of any MTSP family member, preferably from a mammal, including and most preferably human, that, for example, is expressed in tumor cells at different levels from non-tumor cells, and that is not expressed on an endothelial cell. These include, but are not limited to : MTSP1 (or matriptase), MTSP3, MTSP4 and MTSP6.

The specification provides of methods for identification, production, isolation, synthesis and/or purification of MTSP protease domains. The specification states, for example, that MTSP3, MTSP4 and MTSP6 are isolated from any animal, particularly a mammal, and includes but are not limited to, humans, rodents, fowl, ruminants and other animals (see page 20, lines 21-23; page 21, lines 11-13; and page 21, lines 29-31, respectively). Alternative methods for obtaining the MTSP protein than by directly isolating the MTSP protein are also provided. These include synthesis using genomic DNA, chemically synthesizing the gene sequence from a known sequence and making cDNA to the mRNA that encodes the MTSP protein, for example, and inserting the isolated nucleic acids into an appropriate cloning vector (for example, see pages 67-79).

The instant specification clearly describes structurally and functionally known MTSPs. The catalytic function of MTSPs is known in this art. The catalytically active purified single-chain form polypeptide including the protease domain of type II MTSPs or catalytically active portions thereof described in the instant application elicit their effect through these known functions of the protease domains of MTSPs. The activity of the claimed substantially purified single-chain polypeptide including the protease domain of a MTSP or a catalytically active portion thereof is described and demonstrated for the exemplary polypeptides.

The specification also defines structural features and structure-function relationships that identify the claimed genus of polypeptides including a protease domain or catalytically active portion thereof and having serine protease activity. Such description includes information regarding the tertiary structure of MTSPs. For example, the specification teaches the locus of the disulfide bonds, identifies the Cys residues that link the protease domain to the rest of the polypeptide, and teaches that the polypeptide includes at least one of the active site triad, primary specificity pocket and oxyanion hole. The specification states that the serine protease family of proteins shares a high degree of homology. Hence, other related proteins, such as MTSPs from other species, can be readily identified. The specification also teaches that the protease domain of a MTSP shares homology and structural features with the chymotrypsin/trypsin family protease

domains. The previous response and the application establish the application describes MTSP family and describes identification and isolation of protease domains.

In addition, the specification also provides exemplary assays in which catalytic activity of the polypeptides can be tested (for example, see Examples 3 and 4). If necessary, one of skill in the art could test the polypeptides for catalytic activity using the assays provided or known to those of skill in art or to review the sequences to determine which possess the requisite protease domain structure in order to identify those that possess catalytic activity.

In addition, the standard for evaluating written description is based on the knowledge of skill in the art. *In re Gosteli*, 872 F.2d at 1012. As discussed in detail above with respect to MTSPs and the protease domains thereof, the knowledge of one of skill in the art is and was high at the time of filing and before. The claimed polypeptides include an MTSP serine protease domain or catalytically active portion thereof. The protease domain was well known in the art and easily identified by identifying the activation cleavage site in the polypeptide.

The court stated in *Eli Lilly* that the written description requirement can be met by providing relevant identifying characteristics, including structural and physical characteristics, functional characteristics coupled with known or disclosed correlation with structural characteristics to demonstrate that the applicant was in possession of the claimed subject matter. *University of California v. Eli Lilly,* 119 F. 3d 1559, 1568, 43 USPQ2d 1398, 1406 (Fed. Cir. 1997). Applicant does not dispute this standard; this standard has been met. The application describes and provides exemplary members of the MTSP family, and teaches the protease domains thereof and how to identify others.

In *Eli Lilly*, the court stated:

> In claims involving chemical materials, generic formulae usually indicate with specificity what the generic claims encompass. One skilled in the art can distinguish such a formula from others and can identify many of the species that the claims encompass. Accordingly, such a formula is normally an adequate description of the claimed genus.

The recited protease domain is a feature that one of skill in the art can use to identify the claimed polypeptides. As explained in detail above, the MTSP family was a known family; sequences of the full-length proteases were known, numerous members of the family had been identified and characterized. The instant application provides several new members. The presently pending claims are directed to isolated single-chain protease domains, which the

instant application teaches and demonstrates have activity as single chain polypeptides. The instant application provides the sequences of more than a dozen members of the family. Hence, the recitation in the claim that the polypeptides contain a protease domain from an MTSP and are single-chain polypeptides indicates "with specificity what the generic claims encompass. One skilled in the art can distinguish such a formula from others and can identify many of the species that the claims encompass." Therefore, the claims and application satisfy the standard set in *Eli Lilly*.

The Federal Circuit in clarifying the holding of *Eli Lilly* stated "...Eli Lilly did not hold that all functional descriptions of genetic material necessarily fail as a matter of law to meet the written description requirement; rather, the requirement may be satisfied if in the knowledge of the art the disclosed function is sufficiently correlated to a particular, known structure." *Amgen Inc. v. Hoechst Marion Roussel, Inc.*, 314 F.3d 1313, 1332 (Fed. Cir. 2003). As explained, the activation cleavage site that borders the protease domain of an MTSP as well as the structural features of a protease domain were well-known in the art. One skill in the art would recognize that applicant had possess of a protease domains from MTSPs.

The Examiner has failed to indicate why one of skill in the art, in view of the description in the specification of methods for preparing and testing polypeptides for activity and in view of the extensive knowledge of those of skill in the art, would be unable to recognize, upon reading the disclosure, that Applicant invented the claimed subject matter. The specification teaches that numerous members of the MTSP family are known, provides additional members, teaches how to identify and isolate protease domains as single chains and how to assess activity. One of skill in the art could, if needed, readily test any of the those polypeptides for catalytic activity.

Therefore, the combination of the disclosure of the specific chemical structures of at least a dozen species within the scope of the claims as well as teachings in the specification (and knowledge of those of skill in the art) of assays for testing for activity and the evidence that those of skill in the art are very familiar with the serine protease structure and function renders it clear that one of skill in the art would recognized that applicant had possession of the claimed polypeptides. The generic "invention" devolves to a recognition that a single chain isolated form of the protease domain of members of this known family has protease activity. One of skill in the art would have recognized from reading the disclosure that Applicant had possession of this genus as well as numerous species thereof. This teaching and knowledge

coupled with the ability to test for functional mutants with the assays provided for in the specification and known in the art demonstrates that Applicant sufficiently described and was in possession of the polypeptides as claimed, at the effective filing date of the claims.

In light of Applicant's disclosure, one of skill in the art would have recognized from reading the application that Applicant provided single-chain polypeptides with the recited protease domain structure that possess serine protease activity. Given the fact that numerous members of the MTSP family were known at the time of filing, the features of the protease domain of serine protease polypeptides identified in the application and known in the art, coupled with the ability to test polypeptides serine protease activity using assays provided in the application and known in the art, one of skill in the art would recognize that Applicant was in possession of the claimed subject matter at the effective filing date(s) of the claims.

IV. REJECTION OF CLAIMS 1-3, 5-7, 9, 11, 13, 14, 16, 18-20, 34-36, 40-42 AND 137 UNDER 35 U.S.C. §112, FIRST PARAGRAPH – Scope of Enablement

Claims 1-3, 5-7, 9, 11, 13, 14, 16, 18-20, 34-36, 40-42 and 137 are rejected under 35 U.S.C. § 112, first paragraph, because the specification allegedly fails to describe the claimed subject matter in such a way as to enable one skilled in the art to make and use the claimed subject matter commensurate in scope with these claims. The Examiner states that the specification is enabling for a polypeptide that includes amino acids 615-855 of SEQ ID NO:2, amino acids 205-437 of SEQ ID NO:4, amino acids of SEQ ID NO:6 and amino acids 217-443 of SEQ ID NO:112. The Examiner alleges that the specification does not reasonably provide enablement for a polypeptide that includes any protease domain of any type II membrane type serine protease or catalytically portion thereof that include polypeptides with a modification of 40-95% or variants having a free cysteine replaced with a serine residue or a polypeptide with a protease domain having 40-95% sequence identity to amino acids 615-855 of SEQ ID NO:2. It is alleged that it would require undue experimentation for one of skill in the art to make such modified polypeptides with an expectation of success because the result of such modifications in unpredictable. It is further alleged that the claimed polypeptides encompass a large number of polypeptides and yet the specification does not provide sufficient guidance on the nature of the changes that can be tolerated such that the proteins retain activity. In response to Applicant's arguments in the previous Response, evidencing the extensive knowledge in the art with respect to serine proteases, the instant Office Action argues that these arguments are not persuasive because the specification allegedly does not establish (a) regions of the protein structure that may be modified without

affecting MTSP/serine protease activity; (b) the general tolerance of MTSP to modification and extent of such tolerance; (c) a rational and predictable scheme for modifying any amino acid residue (up to 95% of the amino acids) with an expectation of obtaining the desired biological function; and (d) which of the essentially infinite possible choices is likely to be successful. Therefore, the Office Action concludes, it would require undue experimentation to produce claimed polypeptides.

This rejection is respectfully traversed. As discussed below, above and previously, notwithstanding the disclosure of new proteases and individual protease claims, the instant application discloses and claims a generic invention: isolated single-chain protease domains from MTSPs. MTSPs are a well-known family and numerous members are known and disclosed in the application. In addition, the application provides new members. The specification teaches identification, preparation and isolation of protease domains and those of skill in the art, in view of the application, readily can identify and isolate a protease domain from any MTSP. This is a well-characterized family of proteins.

RELEVANT LAW

The discussion of the relevant law from previous responses is incorporated herein.

ANALYSIS

Application of the Factors Enumerated in *In re Wands*

It respectfully is submitted that analysis of enablement requires consideration of all of the "Wands Factors" and that focusing on one or two of the factors is a misapplication of the law. Applicant has discussed application of the "Wands Factors" in the previous responses, and such discussions are incorporated herein by reference. It would not require undue experimentation to isolate single-chain protease domains from any MTSP polypeptide. Further it would not require undue experimentation to make modifications thereto. As amended herein, the claims recite that the polypeptide should possess at least 95% sequence identity to an MTSP protease domain. As discussed in detail below as well as enumerated in the previous Response, a consideration of the factors enumerated in *In re Wands* demonstrates that the application, in conjunction with what was known to one of skill in the art, teaches how to make and use the subject matter as claimed without undue experimentation.

Breadth of the Claims

Claim 1 is directed to an isolated substantially **purified single-chain polypeptide** that includes a **protease domain** of a type-II membrane-type serine protease (MTSP) or a catalytically active fragment thereof. The MTSP protease domain or catalytically active

fragment thereof is the **only portion of the single-chain polypeptide from the MTSP**. Claims 2, 3, 5, 7, 11, 13, 18-20, 34-36 and 40-42 ultimately depend from claim 1 and recite additional features and specific family members.

Claims 13, 14 and 16-20 depend from claim 1. These claims are directed to MTSP polypeptides that include modifications of the exemplified MTSP sequences. For example, the polypeptides of claim 13 incorporate the features of claim 1 and in addition have at least about 95% sequence identity with one of the exemplified MTSP1, MTSP3, MTSP4 and MTSP6 protease domains Claim 34 recites particular polypeptides within the scope of claim 1. Claims 35 and 36 are directed to a conjugates including a polypeptide of claim 1, and a targeting agent linked to the protein directly or via a linker. Claims 40-42 are directed to a solid support including two or more polypeptides of claim 1 linked thereto either directly or via a linker.

Level of Skill

The level of skill in this art is recognized to be high (see, *e.g.*, *Ex parte Forman*, 230 USPQ 546 (Bd. Pat. App. & Int'f 1986)). The numerous articles and patents made of record in this application address a highly skilled audience and further evidence the high level of skill in this art.

Teachings of the Specification

As discussed in the previous response, and above, the specification teaches that MTSP polypeptides constitute a recognized family of serine proteases. For example, page 18, lines 1-23 recites:

> As used herein, "transmembrane serine protease (MTSP)" refers to a family of transmembrane serine proteases that share common structural features as described herein (see, also Hooper et al. (2001) J. Biol. Chem.276:857-860). Thus, reference, for example, to "MTSP" encompasses all proteins encoded by the MTSP gene family, including but are not limited to: MTSP1, MTSP3, MTSP4 and MTSP6, or an equivalent molecule obtained from any other source or that has been prepared synthetically or that exhibits the same activity. Other MTSPs include, but are not limited to, corin, enteropeptidase, human airway trypsin-like protease (HAT), MTSP1, TMPRSS2, and TMPRSS4. Sequences of encoding nucleic molecules and the encoded amino acid sequences of exemplary MTSPs and/or domains thereof are set forth in SEQ ID Nos. 1-12, 49, 50 and 61-72. The term also encompass MTSPs with conservative amino acid substitutions that do not substantially alter activity of each member, and also encompasses splice variants thereof. Suitable conservative substitutions of amino acids are known to those of skill in this art and may be made generally without altering the biological activity of the resulting molecule. Of particular interest are MTSPs of mammalian, including human, origin. Those of skill in this art recognize that, in general, single amino acid substitutions in non-essential regions of a polypeptide do not

> substantially alter biological activity (see, e.g., Watson *et al.* Molecular Biology of the Gene, 4th Edition, 1987, The Bejamin/ Cummings Pub. co., p.224).

The specification teaches that a protease domain from an MTSP polypeptide is active as a single- chain polypeptide. Additionally, smaller fragments of the protease domain also are active as single-chain polypeptides (page 18, line 24-page 19, line 2):

> As used herein, a "protease domain of an MTSP" refers to the protease domain of MTSP that is located within the extracellular domain of a MTSP and exhibits serine proteolytic activity. It includes at least the smallest fragment thereof that acts catalytically as a single chain form. Hence it is at least the minimal portion of the extracellular domain that exhibits proteolytic activity as assessed by standard assays in vitro assays. Those of skill in this art recognize that such protease domain is the portion of the protease that is structurally equivalent to the trypsin or chymotrypsin fold.

The specification further teaches that MTSP protease domains can vary in sequence but that these proteins retain a conserved structure as well as sequence identity to identified MTSP proteins exemplified in the application. For example, see page 19, lines 3-24, which recites:

> Exemplary MTSP proteins, with the protease domains indicated, are illustrated in Figures 1-3, Smaller portions thereof that retain protease activity are contemplated. The protease domains vary in size and constitution, including insertions and deletions in surface loops. They retain conserved structure, including at least one of the active site triad, primary specificity pocket, oxyanion hole and/or other features of serine protease domains of proteases. Thus, for purposes herein, the protease domain is a portion of a MTSP, as defined herein, and is homologous to a domain of other MTSPs, such as corin, enteropeptidase, human airway trypsin-like protease (HAT), MTSP1, TMPRSS2, and TMPRSS4, which have been previously identified; it was not recognized, however, that an isolated single chain form of the protease domain could function proteolytically in *in vitro* assays. As with the larger class of enzymes of the chymotrypsin (S1) fold (see, e.g., Internet accessible MEROPS data base), the MTSPs protease domains share a high degree of amino acid sequence identity. The His, Asp and Ser residues necessary for activity are present in conserved motifs. The activation site, which results in the N-terminus of second chain in the two chain forms is has a conserved motif and readily can be identified (see, e.g., amino acids 801-806, SEQ ID No. 62, amino acids 406-410, SEQ ID No. 64; amino acids 186-190, SEQ ID No. 66; amino acids 161-166, SEQ ID No. 68; amino acids 255-259, SEQ ID No. 70; amino acids 190-194, SEQ ID No. 72).

The application describes the protease domain of a number of MTSP family members including MTSP1, MTSP3, MTSP4 and MTSP6 as well as HAT, corin, enteropeptidase, TMPRSS4 and TMPRSS2. Identification of the protease domain from an MTSP regions merely requires identification of the activation cleavage site and several other structural features as outlined. The locus of the protease domain in the known MTSP family members is known, and the instant application provides protease domains from several other family members. A comparison of sequence identity among family members (see e.g. Figure 4 of the application) reveals that the protease domains share conserved sequences, including the

catalytic triad of His, Asp and Ser residues and their surrounding conserved motifs. Additionally, the specification demonstrates that MTSP protease domains can have a reasonable amount of sequence variation and yet retain serine protease activity. MTSP1, MTSP3, MTSP4 and MTSP6 protease domains share about 40% sequence identity with each other. The specification teaches that each of these protease domains is an example of an MTSP protease domain that has activity in the single chain form.

The specification also teaches additional modifications. For example, see page 26, lines 13-25, which recites:

> Hence smaller portions of the protease domains, particularly the single chain domains, thereof that retain protease activity are contemplated. Such smaller versions will generally be C-terminal truncated versions of the protease domains. The protease domains vary in size and constitution, including insertions and deletions in surface loops. Such domains exhibit conserved structure, including at least one structural feature, such as the active site triad, primary specificity pocket, oxyanion hole and/or other features of serine protease domains of proteases. Thus, for purposes herein, the protease domain is a single chain portion of an MTSP, as defined herein, but is homologous in its structural features and retention of sequence of similarity or homology the protease domain of chymotrypsin or trypsin. Most significantly, the polypeptide will exhibit proteolytic activity as a single chain.

The specification teaches that included in the conserved features of MTSP protease domain polypeptides is a catalytic triad as well as the activation cleavage site, which defines the terminus of the protease domain polypeptides when they are isolated as single chain polypeptides.

The specification explains that beyond such conserved features the polypeptides are tolerant of modification. The specification explains that such modifications can be effected using numerous methods known in the art. For example, at page77, line 17 through page 78, line 11, the specification states:

> A variety of modifications of the MTSP proteins and domains are contemplated herein. An MTSP-encoding nucleic acid molecule be modified by any of numerous strategies known in the art (Sambrook *et al.*, 1990, Molecular Cloning, A Laboratory Manual, 2d ed., Cold Spring Harbor Laboratory, Cold Spring Harbor, New York). The sequences can be cleaved at appropriate sites with restriction endonuclease(s), followed by further enzymatic modification if desired, isolated, and ligated in vitro. In the production of the gene encoding a domain, derivative or analog of MTSP, care should be taken to ensure that the modified gene retains the original translational reading frame, uninterrupted by translational stop signals, in the gene region where the desired activity is encoded.
>
> Additionally, the MTSP-encoding nucleic acid molecules can be mutated in vitro or in vivo, to create and/or destroy translation, initiation, and/or termination sequences, or to create variations in coding regions and/or form new restriction endonuclease sites

> or destroy pre-existing ones, to facilitate further in vitro modification. Also, as described herein muteins with primary sequence alterations, such as replacements of Cys residues and elimination of glycosylation sites are contemplated. Such mutations may be effected by any technique for mutagenesis known in the art, including, but not limited to, chemical mutagenesis and in vitro site-directed mutagenesis (Hutchinson *et al.*, J. Biol. Chem. 253:6551-6558 (1978)), use of TAB® linkers (Pharmacia). In one embodiment, for example, an MTSP protein or domain thereof is modified to include a fluorescent label. In other specific embodiments, the MTSP protein is modified to have a heterofunctional reagent, such heterofunctional reagents can be used to crosslink the members of the complex.

The specification exemplifies variation in MTSP sequences. For example the specification provides exemplary MTSP1, MTSP3, MTSP4 and MTSP6 sequences. The specification explains that MTSP1 and MTSP3 amino acid sequences have about 43% identity with each other (for example, see page 162, lines 1-2). The specification also discloses that MTSP1 and MTSP4 have about 37% amino acid sequence identity (for example, see page 167, lines 25-29). The specification also teaches that MTSP4 and MTSP6 share about 60% amino acid sequence identity (for example, see page 172, lines 4-9). The specification teaches that each of the protease domains of these MTSP family members is active as single chain that contains only the protease domain or a smaller catalytically active portion of the protease domain (see, for example at page 20, lines 1-6). Hence, the specification teaches that MTSP protease domains share about 40%-60% and greater sequence identity and are active as single chain polypeptides.

The specification teaches additional modifications of the MTSP polypeptides. For example, the specification explains that for each individual MTSP, the polypeptides can include about 60% amino acid sequence identity with the exemplified MTSP. Such modified polypeptides exhibit serine protease activity as single chain polypeptides. The specification provides exemplary modifications including conservative amino acid substitution (for example, see page 10, lines 3-13) and modifications of cysteine residues and/or of glycosylation sites (for example, see page 78, lines 1-7). The specification also discloses that non-natural amino acids can be introduced as a substitution or addition in the MTSP polypeptides (for example, see page 79, lines 10-21).

Knowledge of those of skill in the art

As discussed above, at the time of filing of the application and before, those of skill in the art were very familiar with serine proteases generally, and with the MTSP family in particular. There was a large body of literature directed to serine proteases and there was general understanding of their structures and requisites for activity (see for example, Hooper *et al.* *J.*

Biol. Chem. 276:857-860, Nienaber *et al.* (2000) *J. Biol. Chem.* 275:7239-48; Sommerhoff *et al.* (1999) *Proc. Natl. Acad. Sci. USA* 96:10984-91; Lu *et al.* (1999) J. Mol. Biol. 292:361-73; Xu *et al.* (2000) *J. Biol. Chem.* 275:378-385, Lin *et al.*(1999) *J. Biol. Chem. 274*: 18231-36 and Bryan (2000) *Biochem. Biophys. Acta 1543*:200-03). These references detail the existing crystal structures, structural comparisons and structural similarities of serine proteases.

This extensive knowledge also is evidenced, for example, in the application as filed and in the literature made of record in the submitted Information Disclosure Statements. As noted in the application, the Type II Serine Proteases family (TTSPs), also referred to as MTSPs, were known (for example, see pages 4-5). Serine proteases are a family that can be distinguished from many other types of proteins and enzymes because they have highly conserved structures (see *e.g.*, Lin *et al.* (1999) *J. Biol. Chem. 274*:18231-36 and Yan *et al.* (1999) *J. Biol. Chem. 274*:14926-35). Moreover, it was known at the time of filing, there is a known correlation between retention of the catalytic triad and retention of serine protease activity. Hence, available to one of skill in the art was the knowledge that serine protease activity could be retained in a serine protease by retaining the conserved structure of the catalytic triad (see for example, Carter *et al.* (1988) *Nature 332:*564-68. Sprang *et al.* (1987) Science 237:905-09, Craik *et al.* (1987) Science 237:909-13 and Bachovchin *et al.* (1981) *Proc. Natl Acad. Sci. 78*: 7323-26). In addition, other features were identified at the time of filing as highly conserved features in serine proteases including a cleavage site at the N-terminus of the protease domain, a substrate specificity pocket in the protease domain and conserved cysteines that participate in disulfide bonding (see for example, Figure 4 and page 18235 of Lin *et al.* and Figure 2 and page 18236 of Yan *et al.*) Hence, the requisites for retention of serine protease activity are well-known and characterized and were available at the effective filing date of the claimed subject matter. Hence, a wide variety of structural information on serine proteases was well-known in the art.

Furthermore, the instant claims only require identification of the protease domain of an MTSP, and its isolation as a single chain polypeptide. A number of MTSPs were known and the locus of the protease domain identified. Those of skill in the art can readily identify the protease domain region in an MTSP, and, if necessary test it for the protease activity.

The methods and guidance for comparing amino acid sequences to generate and confirm sequences with sequence identity to an MTSP polypeptide sequence such as SEQ ID NOS: 2, 4, 6 and 12 was available in the art at the time of filing the instant application. As described in the instant specification, computer algorithms such as the "FAST A" program,

using for example, the default parameters as in Pearson *et al.* (1988) Proc. Natl. Acad. Sci. USA 85:2444 were available. Other available programs include the GCG program package (Devereux, J., *et al.* , Nucleic Acids Research 12(I):387 (1984)), BLASTP, BLASTN, and FASTA (Atschul *et al.*, J Molec Biol 215:403 (1990); *Guide to Huge Computers*, Martin J. Bishop, ed., Academic Press, San Diego, 1994, and Carillo *et al.* (1988) SIAM J Applied Math 48:1073). In addition, methods for generating nucleotide and protein sequence variation were widely available in the art. Thus, one of skill in the art could use such programs with a serine protease sequence, for example, to align the sequence and identify the structural features of importance for retention of activity and use the methods for generating sequence variation to make the identified protein variants. The Examiner states that enzyme isolation techniques and recombinant and mutagenesis techniques are well known.

Methods for assaying protease activity including protease specificity, level of activity and response to inhibitors was well known in the art (see, for example, Lu *et al.* (1999) J. Mol. Biol. 292:361-73; Xu *et al.* (2000) *J. Biol. Chem.* 275:378-385). Methods for high throughput assays and detection were also widely available (See generally, *High Throughput Screening: The Discovery of Bioactive Substance*s (Devlin, Ed.) Marcel Dekker, 1997; Sittampalam *et al., Curr. Opin. Chem. Biol.*, 1:384-91 (1997); and Silverman *et al., Curr. Opin. Chem. Biol.*, 2:397-403 (1998)). Hence, the amount of knowledge of those of skill in the art was extensive and the requisite structural and functional features required for protease activity was well known.

The Examiner states that the specific amino acid positions within a protein's sequence where amino acid modification can be made with a reasonable expectation of success in obtaining the desired activity are limited in any protein and the result of such modifications is unpredictable. Applicant respectfully disagrees in the case of the family of serine proteases. The previous response, the art and the application establish that serine proteases are well known in the art and the structural requirements for activity are known and that the instantly claimed polypeptides share sequence homology with the chymotrypsin/trypsin family for which tertiary structures are known. The specification also provides exemplary assays for testing catalytic activity of the polypeptides and also provides descriptions of how to assess percentage identity and teaches that these techniques were well known in the art. The specification also teaches conserved characteristics among serine proteases.

Furthermore, the MTSPs are a known family of serine proteases, and the protease domain of any member can be readily identified. As amended, the claims specifically recite

variations of only 5%, far less than the variations observed among the dozen plus members provided in the application.

Further, since the complete sequences of at least a dozen MTSP polypeptides are set forth in the specification, one of skill in the art using routine methods can clearly identify all of the protease domains as well as all polypeptides whose protease domain possesses at least 95% sequence identity to any of the disclosed polypeptides or to any other MTSP. There is no need for the specification to set forth all of the polypeptides that possess 95% sequence identify.

The Examiner states that recombinant and mutagenesis techniques and enzyme isolation techniques are known and that it is routine to screen for multiple substitutions or multiple modifications as encompassed by the instant claims (see Office Action, page 11). If needed, one of skill in the art can test polypeptides for catalytic activity by routine experimentation using the assays provided in the specification or known to those of skill in art.

Contrary to the Examiner's position, one of skill in the art would conclude that such a description in the specification constitutes a sufficiently detailed description of identifying characteristics of the claimed subject matter consistent with *Enzo* (supra), particularly in view of the fact that these proteins are members of the well-characterized serine protease family of proteins. In fact, related family members are in the art, which is of record. Such members were identified solely based upon sequence characteristics and they diverge from the instantly claimed polypeptides by more than 70%.

Working Examples

The application provides working examples that demonstrate each of the features of the claimed polypeptides. For instance, the Examples provide detailed guidance for identify and isolating MTSP protease domains. Example 1 describes the cloning of and identification of MTSP3 based on its sequence similarity with MTSP1. Example 2 describes the identification and cloning of two MTSP4 polypeptides, MTSP4-S and MTSP4-L. Example 3 describes the identification and cloning of an MTSP6 polypeptide based on sequence similarity to MTSP4. In each case, an MTSP polypeptide sequence is identified that includes a protease domain with a cleavage site and a catalytic triad (see, e.g., Figure 4). As noted, for example, in Example 1, identification of MTSP3 as a serine protease required only 43% sequence identity. Similarly, Example 2 demonstrates that 37% sequence identity with MTSP1 was sufficient to identify MTSP4.

The Examples demonstrate additional features of the claimed polypeptides. For example, Examples 1, 2, 3 and 6 each demonstrate the expression of MTSP polypeptides in normal and tumor tissues. The working examples further demonstrate that each of the MTSP polypeptides, having, for example, 37-43% sequence identity, is active as a single chain protease domain.

The Examples demonstrate expression of single chain protease domains. For example, Example 1 describes the cloning of MTSP3 into an expression vector and expressing it in *E. coli*. The example describes the purification of the protein and the serine protease activity of the single chain protease domain using a variety of substrates. Examples 4 and 5 describe additional expression vector cloning techniques for *Pichia pastoris* expression for MTSP 3, 4 and 6. Example 5 provides a detailed example of a serine protease assay for the expressed MTSP6 single chain protease domain. Examples 6 and 7 provide a detailed description of the cloning, expression and purification of an MTSP1 single chain protease domain. Example 8 provides detailed serine protease assays for MTSP1. Additionally, Example 1 demonstrates that additional sequence variation can be introduced into single chain protease domains of an MTSP, such as a cysteine to serine change, without altering serine protease activity. Hence, the examples demonstrate the ability of one of skill in the art to isolate and express MTSP single chain polypeptides that include the protease domain without additional regions of MTSP sequence. The examples further demonstrates that one of skill in the art can identify MTSP sequences with 37-43% sequence identity that share common features of an MTSP and are active as single chain polypeptides.

As discussed in a number of places above, the application provides the sequences and identities of at least a dozen MTSP family members and describes identification of the protease domain. One of skill in the art can readily isolate a protease domain as a single chain from any MTSP family member.

Predictability

The predictability at issue herein is whether one of skill in the art could isolate protease domains from MTSP family members and variants thereof that differ in less than 5% of the amino acids, include family members that are single chain protease domains that have at least about 95% sequence identity with an MTSP1 protease domain that includes the sequence of amino acids set forth as residues 615-855 in SEQ ID NO:2, as amino acids 205-437 in SEQ ID NO:4, as the amino acid residues in SEQ ID NO:6 or as amino acids 217-443 of SEQ ID NO:12, or variants that differ in only 5% of the residues. Applicant respectfully

submits that one of skill in the art, given the instant disclosure, could predictably make such polypeptides as the MTSP family is well known and the sequences of exemplary new family members, as well as known members, are provided in the application. One of skill in the art could readily make minor amino acid variation there, and, if needed, test such polypeptide variants for serine protease activity.

In contrast to the allegations of "unpredictability" set forth in the Office Action, the specification and the knowledge in the art evidence many factors of *predictability* with respect to MTSP polypeptide variants. First, the specification provides more than a dozen exemplary polypeptides. These are defined chemical structures from which one of skill in the art is given a reference point. As explained above, included among exemplary polypeptides are MTSP1, MTSP3, MTSP4-S, MTSP4-L and MTSP6, which share about 40% sequence identity. The specification demonstrates, however, that these MTSP polypeptides share conserved features including a protease domain with a catalytic triad and N-terminal activation cleavage site. Furthermore, the specification teaches isolation of the protease domains as single chains and demonstrates that they possess proteolytic activity.

Second, the specification delineates structural and functional features of the protein. These features identify key regions and residues that one of skill in the art would know to conserve in order to retain serine protease activity. These features also provide reference points for alignments with other known serine proteases. These features also allow one of skill in the art to make further structure-function correlations, again providing predictable correlations of regions and residues to conserve or change. As evidenced by the references cited in the specification and in the Information Disclosure Statements of record in this application, a large body of knowledge pertaining to structure-function relationships of serine proteases was known in the art. In addition, the specification provides exemplary assays to assess serine protease activity, including a variety of substrates for MTSP activity. Additional serine protease assays were available in the art at the time of filing the instant application. One of skill in the art could readily and routinely test any MTSP family member protease domain or a variant thereof for serine protease activity as a single chain protease.

As taught in the specification as well as evidenced by the art of record, maintenance of the catalytic triad is sufficient to retain serine protease activity. Therefore, one of skill in the art could make and generate MTSP family member protease domains as well as variants of MTSP protease domains with at least 95% identity. Serine protease activity of these variants could easily and routinely be confirmed using the assays provided in the application

and known in the art. The routine manipulations to identify and isolate an MTSP protease domain as a single chain as well as to generate minor variants thereof, *e.g.* selecting non-catalytic triad residues and aligning variant sequences to confirm at least about 95% identity, are not unpredictable. The Examiner states that enzyme isolation techniques and recombinant and mutagenesis techniques are known and that it is routine to screen for multiple substitutions or multiple modifications as encompassed by the instant claims (see Office Action, page 11).

The experimentation necessary to make and use MTSP polypeptides, as described above, is routine. "Enablement is not precluded by the necessity for some experimentation such as routine screening. experimentation needed to practice the invention must not be undue experimentation. 'The key word is undue, not experimentation.' " *In re Wands*, 858 F.2d at 737-38 (quoting *In re Angstadt*, 537 F.2d at 504; emphasis added; additional internal citations omitted). The art related to serine proteases also demonstrates that such experimentation is not undue. For example, Pearson *et al.* ((1997) *Cabios Invited Review 13(4)*: 325-32) explains that serine proteases share a conserved catalytic site, the catalytic triad. In addition, trypsin-like serine proteases have several diagnostic motifs throughout the protein including a conserved protein fold and anti-parallel β barrel structures that contribute to the function of the protease. Pearson *et al.* states that one could recognize proteins that have protease activity based on these conserved structures. Hence, generation of variants with serine protease activity is routine because one of skill in the art can use such conserved features as a guide for designing the location of variations to maintain these features. In addition, Cheah *et al.* ((1990) *J. Biol. Chem. 265*:7180-7187) provides a demonstration of the predictability of generating variants of serine proteases based on an exemplary sequence. The authors use known structural and functional information about trypsin-like serine proteases to obtain mutations in a rhinovirus 3C protease with predicted functional phenotypes. Thus, the art available at the time of filing, and before, demonstrates that one of skill in the art could make variants of a serine protease in a predictable manner.

Therefore, one of skill in the art could make protease domains as single chains from an MTSP family member and also generate variants of MTSP polypeptides with at least about 95% identity/ Activity of the single chain protease domains and the minor variants thereof could easily and routinely be confirmed using the assays provided in the application and known in the art. The routine manipulations to generate an MTSP single chain protease domains are not unpredictable.

The instant application identifies MTSP polypeptides that possess serine protease activity as a single chain. Such demonstration of single chain activity had not been demonstrated before the instant application. The application provides adequate description to demonstrate that a common feature among the MTSP family members is the activity of a single chain form that includes the protease domain or catalytically active portions thereof in the absence of other MTSP portions. The application provides exemplary MTSP's that share about 40% sequence identity and possess such features. Therefore, the specification demonstrates that by following the teachings of the application, one of skill in the art can predictably identify, make and use MTSP protease domains.

Conclusion

In light of the breadth of the claims, the extensive teachings and examples in the specification, the high level of skill of those in this art, the knowledge of those of skill in the art, and the fact that it is predictable to identify protease domains in MTSP family members and prepare single chain forms thereof as well as variants with at least 95% sequence identity, it would not require undue experimentation for one of skill in the art to make and use polypeptides with the features as claimed. Accordingly, a consideration of the factors enumerated above leads to the conclusion that, based on the disclosure in the specification, undue experimentation would not be required to make and use polypeptides as instantly claimed.

PUBLIC POLICY CONSIDERATIONS

It would be unfair, unduly limiting and contrary to the public policy upon which the patent laws are based to require Applicant to limit the instant claims to only an exemplified MTSP protease domain. To limit an Applicant to claims involving only one exemplified protease domain would permit a competitor, seeking to avoid infringement to merely follow the disclosure and make routine substitutions. Thos "is contrary to the purpose for which the patent system exists - to promote progress in the useful arts"). See, *e.g.*, *In re Goffe*, 542 F.2d 801, 166 USPQ 85 (CCPA 1970).

> The public purpose on which the patent law rests requires the granting of claims commensurate in scope with the invention disclosed. This requires as much the granting of broad claims on broad inventions as it does the granting of more specific claims on more specific inventions" *In re Sus and Schafer*, 49 CCPA 1301, 306 F.2d 494, 134 USPQ 301, at 304.

To require Applicant to so-limit the claims would permit those of skill in the art to practice what is disclosed in the specification but avoid infringing claims so-limited. To

permit that is simply not fair. The instant application teaches that the single-chain protease domains of MTSP family members possess protease activity as single chain polypeptides. The specification demonstrates this and provides a variety of examples. Those of skill in the art can readily identify protease domains in an MTSP family member and isolate it. Those of skill in the art should not be permitted to do so and avoid infringing the claims. Thus, given the broad teachings in the application of a genus of polypeptides, Applicant is entitle to claims that reflect such broad teachings.

V. REJECTION OF CLAIMS UNDER 35 U.S.C. §102

A. THE REJECTION OF CLAIMS 1-3, 5-7, 9 and 34-36 UNDER 35 U.S.C. §102(a)

Claims 1-3, 5-7, 9 and 34-36 are rejected under 35 U.S.C. § 102(a) as anticipated by Takeuchi *et al.* (Proc. Natl. Acad. Sci. USA 96: 11054-11061 (1999)) because Takeuchi *et al.* allegedly discloses a serine protease that is 100% identical to amino acids 615-855 of SEQ ID NO:2, is not expressed on normal endothelial cells, is of human origin, consists essentially of the protease domain having catalytic activity and is expressed on tumor cells. The Examiner states that a full-length MTSP1 of Takeuchi *et al.* anticipates the instant claims. The bases set forth by the Examiner are discussed in turn below. This rejection is respectfully traversed.

RELEVANT LAW

Anticipation requires the disclosure in a single prior art reference of each element of the claim under consideration. *In re Spada*, 15 USPQ2d 1655 (Fed. Cir, 1990), *In re Bond*, 15 USPQ 1566 (Fed. Cir. 1990), *Soundscriber Corp. v. U.S.*, 360 F.2d 954, 148 USPQ 298, 301, adopted 149 USPQ 640 (Ct. Cl.) 1966. See, also, *Richardson v. Suzuki Motor Co.*, 868 F.2d 1226, 1236, 9 USPQ2d 1913,1920 (Fed. Cir.), cert. denied, 110 S.Ct. 154 (1989). "[A]ll limitations in the claims must be found in the reference, since the claims measure the invention." *In re Lang*, 644 F.2d 856, 862, 209 USPQ 288, 293 (CCPA 1981). It is incumbent on Examiner to identify wherein each and every facet of the claimed invention is disclosed in the reference. *Lindemann Maschinen-fabrik Gmbh v. American Hoist and Derrick Co.*, 730 F.2d 1452, 221 USPQ 481 (Fed. Cir. 1984). Further, the reference must describe the invention as claimed sufficiently to have placed a person of ordinary skill in the art in possession of the invention. An inherent property has to flow naturally from what is taught in a reference. *In re Oelrich*, 666 F.2d 578, 581, 212 USPQ 323, 326 (CCPA 1981).

"Rejections under 35 U.S.C. §102 are proper only when the claimed subject matter is identically disclosed or described in the 'prior art' . . . the [r]eference must clearly and unequivocally disclose the claimed compound or direct those skilled in the art to the compound without *any* need for picking, choosing, and combining various disclosures not directly related to each other by the teachings in the cited references. Such picking and choosing may be entirely proper when making a rejection of a §103, obviousness rejection, where the applicant must be afforded an opportunity to rebut with objective evidence any inference of obviousness which may arise from the *similarity* of the subject matter which he claims to the prior art, but it has no place in the making of a §102, anticipation rejection." (Emphasis in original). *In re Arkey, Eardly, and Long*, 455 F.2d 586, 172 USPQ 524 (CCPA, 1972).

THE CLAIMS

Claim 1 is directed to an isolated substantially purified single-chain polypeptide that includes a protease domain of a type-II membrane-type serine protease (MTSP) or a catalytically active fragment thereof. The MTSP protease domain or catalytically active fragment thereof is the only portion of the single-chain polypeptide from the MTSP, the MTSP protease domain or catalytically active fragment thereof has serine protease activity. Claims 3, 5, 34-36, 40 and 41 depend from claim 1 and recite additional features..

Disclosure of Takeuchi *et al.*

Takeuchi *et al.* discloses a polypeptide that contains 855 amino acids and is designated MT-SP1. This protein has sequence identity with the full-length MTSP1 set forth as SEQ ID NO:2 of the instant application. Takeuchi *et al.* discloses an expression vector that includes the protease domain and nucleotides of the pro-domain (see page 11055, left col., third full paragraph). Takeuchi *et al.* discloses expressing its polypeptide in *E. coli* X-90 (page 11055, col. 2, 4th full paragraph). Takeuchi *et al.* discloses that its expression vector includes the mature protease domain and a small portion of the pro-domain and was designed to over-express the sequence encoding a polypeptide containing amino acids 596-855 with a His-tag fusion to produce as a construct Met-Arg-Gly-Ser-His_6-aa596-855 (page 11055, column 2, third full paragraph). Takeuchi *et al.* identifies the locus of the MT-SP1 protease domain (amino acids 615-855; see Fig. 4, page 11058) in the longer protein, but does not disclose its isolation as a single chain. Takeuchi *et al.* discloses that the pro-domain region is disulfide bonded to the protease domain of its construct (page 11055, column 2, third full paragraph). Takeuchi *et al.* discloses that amino acids Cys 604 and Cys 731 are disulfide bonded (see for example, at page 11060, col.1) and that the pro-domain is disulfide bonded to the protease

domain (see Figure 4). Takeuchi *et al.* does not disclose, teach or suggest isolation of a single chain form of the protease domain. Therefore Takeuchi *et al.* does not anticipate any of the rejected or pending claims.

B. Claims

As noted claim 1 is directed to an isolated substantially purified single-chain polypeptide that includes a protease domain of a type-II membrane-type serine protease (MTSP) or a catalytically active fragment thereof, where the MTSP protease domain or catalytically active fragment thereof is the only portion of the single-chain polypeptide from the MTSP, the MTSP protease domain or catalytically active fragment thereof has serine protease activity. The remaining rejected claims are dependent on claim 1. Claim 2, for example, recites that the MTSP is not expressed on endothelial cells. Claims 3, 5 and 34 depend from claim 1 and are directed to various embodiments thereof

C. Analysis - Takeuchi et al. does not anticipate the claimed subject matter

1. Protease domain or catalytically active portion thereof is the only MTSP portion

An element of the pending claims is that the isolated substantially purified polypeptide includes a protease domain or a smaller catalytically active portion of the protease domain as the only portion of the polypeptide from an MTSP. The polypeptides disclosed by Takeuchi *et al.* include additional portions from its MT-SP1. For example, Figure 1 of Takeuchi *et al.* depicts the predicted protein sequence of its full length MT-SP1. The full-length MT-SP1 polypeptide disclosed by Takeuchi *et al.* includes LDLR repeats (453-487) and CUB domains (213-339) in addition to the protease domain (see FIG. 4). Hence, it is not a polypeptide in which the only MTSP portion of the polypeptide is a protease domain or a smaller catalytically active portion of the protease domain.

Takeuchi *et al.* also discloses a polypeptide construct that includes the protease domain, a His-tag and *a portion of the pro-domain*, and refers to this construct as its "purified protease domain." Takeuchi *et al.* discloses that its "purified protease domain" includes the His-tag sequence, stating that a monoclonal antibody directed against the N-terminal Arg-Gly-Ser-His_4 epitope is immunoreactive with its purified protein (see page 11058). Takeuchi *et al.* also discloses that its protease domain has an amino acid sequence containing amino acids 615-855 (numbering as set forth in FIG. 1), and that its polypeptide construct is a His-tag fusion product that contains amino acids 596-855 (as set forth in FIG. 1). Hence, the polypeptide construct disclosed by Takeuchi *et al.* includes a sequence of 19 amino acids (a portion of the pro-domain) from the MTSP other than the protease domain. Takeuchi *et al.*

discloses that this pro-domain region is disulfide bonded to the protease domain (see page 11058, col. 1 and page 11060, col. 1, first paragraph) and remains bonded to the protease domain after activation (page 11058, lines 8-9). Hence, the purified His-tagged protease domain of Takeuchi *et al.* includes MTSP portions other than the protease domain. Furthermore, this polypeptide is a two-chain polypeptide. Thus Takeuchi *et al* does not disclose a single chain polypeptide nor a polypeptide containing a protease domain that is the only portion of the single chain polypeptide from the MTSP.

2. The claimed polypeptide is a single chain polypeptide

Another element of the claimed subject matter is that the polypeptide contains the protease domain or a smaller catalytically active portion thereof and is a single-chain polypeptide. Takeuchi *et al.* discloses that its polypeptide includes the pro-domain and that the pro-domain is cleaved during auto-activation, resulting in a protease domain disulfide bonded to a pro-domain resulting in a two-chain form. Takeuchi *et al.* discloses that the pro-domain remains disulfide bonded to the protease domain after purification (see page 11058). Thus, Takeuchi *et al.* does not disclose an ***isolated substantially purified single-chain*** polypeptide that includes ***as the only portion from the MTSP*** a protease domain or catalytically active portion thereof.

Takeuchi *et al.* discloses that the His-tag portion of its protein (Met-Arg-Gly-Ser-His_6-aa596-855) is cleaved during activation (page 11057, col. 2, last paragraph), which would produce the polypeptide aa596-855. As discussed above, amino acids 596-614 are part of the pro-domain and are not part of the protease domain. Takeuchi *et al.* discloses that under non-reducing conditions the pro-domain is disulfide bonded to the protease domain. Takeuchi *et al.* discloses analysis of its protein using SDS/PAGE to assess activation cleavage. Under the conditions of SDS/PAGE, the disulfide bonding of the protease domain to the pro-domain would be eliminated, producing two separate chains. Because of its size, the liberated pro-domain chain migrates through the gel, and appears to be outside of the visual range of the gels shown in Fig. 6. Takeuchi *et al.* does not disclose isolating the polypeptide of the lower band in Fig. 6A from the gel. Hence, Takeuchi *et al.* does not disclose an isolated, substantially purified single-chain polypeptide where the protease domain or a smaller catalytically active portion thereof has serine protease activity as a single-chain.

3. Conclusion

As discussed above, Takeuchi *et al.* does not disclose an isolated substantially purified single chain polypeptide that contains a protease domain of an MTSP where the protease

domain or a smaller catalytically active portion thereof is the only portion of the single chain polypeptide from the MTSP. Thus, Takeuchi *et al.* does not disclose every element of claim 1. Therefore, Takeuchi *et al.* does not anticipate claim 1 nor any claim dependent thereon.

B. THE REJECTION OF CLAIMS 11-14 and 34 UNDER 35 U.S.C. §102(b)

Claims 11-14 and 34 are rejected under 35 U.S.C. §102(b) as anticipated by Takeuchi *et al.* because it is alleged that the reference discloses a serine protease domain that is 100% identical to amino acids 615-855 of SEQ ID NO:2 where the serine protease domain is identical to the protease domain of SEQ ID NO:2. This rejection is respectfully traversed.

Relevant Law

See above.

The Claims

Claims 11-13 and 34 each depend from claim 1 and therefore incorporate the features of claim 1 as described in detail above. Claim 14 is cancelled herein. Claims 11-13 and 34 recite species of polypeptides with particular MTSP portions and with recited identity and/or homology to recited MTSP sequences.

The disclosure of Takeuchi *et al.*

See above.

Analysis

Anticipation requires the disclosure in a single prior art reference of each element of the claim under consideration. As discussed above in detail, Takeuchi *et al.* fails to disclose any isolated substantially purified single-chain polypeptides that include a protease domain of a type-II membrane-type serine protease (MTSP) or a catalytically active fragment thereof, where the MTSP protease domain or catalytically active fragment thereof is the only portion of the single-chain polypeptide from the MTSP, the MTSP protease domain or catalytically active fragment thereof has serine protease activity and the MTSP is not expressed on endothelial cells.

Merely pointing out the locus in the full-length protein that corresponds to the protease domain does not constitute disclosure of ***in isolated single chain protease domain.*** Takeuchi *et al.* does not disclose, teach or even suggest isolating a single chain polypeptide that contains only amino acids 615-855. Takeuchi *et al.* specifically teaches inclusion of the pro-domain to produce a two-chain polypeptide. The fact that one can point to a longer polypeptide and note the locus of the a domain thereof, does not constitute isolation of the

domain. Takeuchi *et al.* simply does not disclose an **isolated single chain polypeptide that contains only amino acids 615-855 as the MTSP portion of the polypeptide.** The isolated polypeptides disclosed by Takeuchi *et al.* contain additional MT-SP1 polypeptide. Hence, Takeuchi *et al.* does not anticipate claim 1 nor any claim dependent thereon.

VII. THE REJECTION OF CLAIMS 1-3, 5-7, 9, 11-14 and 34 UNDER 35 U.S.C. §102(e)/103(a)

Claims 1-3, 5-7, 9, 11-14 and 34 are rejected under 35 U.S.C. §102(e) as anticipated by O'Brien *et al.* or in the alternative obvious over O'Brien *et al.*, because it is alleged that the reference discloses a polypeptide with 100% identity to full-length MTSP1 as set forth in SEQ ID NO:2 of the instant application. It is further alleged that the polypeptide disclosed by O'Brien *et al.* inherently possess the features set forth in claims 2-3 and 6-9 of the instant application. The Office Action also alleges that the reference discloses a protease domain identified therein as SEQ ID NO:14 that is 100% identical to amino acids 615-855 of SEQ ID NO:2. The Examiner states that O'Brien *et al.* does not disclose purifying the protease yet the Office Action concludes that the disclosed sequences in O'Brien *et al.* anticipate the claimed subject matter

In the alternative, it is alleged that the claims are obvious over the claimed subject matter because O'Brien *et al.* teaches a method of expressing polypeptides in host cells. It also is alleged that the reference teaches that the protease domain could be released from the polypeptide and used as a diagnostic that has the potential for therapeutic intervention. Thus, the Office Action concludes that it would have been obvious to one of skill in the art to express the protease domain disclosed as SEQ ID NO:14 by O'Brien *et al.* and purify the polypeptide. It is alleged that the motivation to make such polypeptides is the disclosed use as a diagnostic for therapeutic intervention. Further, it is alleged that one of ordinary skill in the art would have had a reasonable expectation of success since the expression of heterologous polypeptides was routine in the art and O'Brien *et al.* teaches how to express heterologous polypeptides. This rejection is respectfully traversed.

Relevant Law

With respect to anticipation, the relevant law is set out above. Addressing obviousness, in order to set forth a prima facie case of obviousness under 35 U.S.C. § 103:

(1) there must be some teaching, suggestion or incentive supporting the combination of cited references to produce the claimed invention *(ACS Hospital Systems, Inc. v. Montefiore Hospital*, 732 F.2d 1572, 1577, 221 USPQ 329, 933 (Fed. Cir. 1984)) and

(2) the combination of the cited references must actually teach or suggest the claimed invention.

Further, that which is within the capabilities of one skilled in the art is not synonymous with that which is obvious. *Ex parte Gerlach*, 212 USPQ 471 (Bd. APP. 1980). Obviousness is tested by "what the combined teachings of the references would have suggested to those of ordinary skill in the art." *In re Keller*, 642 F.2d 413, 425, 208 USPQ 871, 881 (CCPA 1981), but it cannot be established by combining the teachings of the prior art to produce the claimed invention, absent some teaching or suggestion supporting the combination (*ACS Hosp. Systems, Inc. v Montefiore Hosp.*, 732 F.2d 1572, 1577. 221 USPQ 329, 933 (Fed. Cir. 1984)). "To imbue one of ordinary skill in the art with knowledge of the invention in suit, when no prior art reference or references of record convey or suggest that knowledge, is to fall victim to the insidious effect of a hindsight syndrome wherein that which only the inventor taught is used against its teacher." *W.L. Gore & Associates, Inc. v. Garlock Inc.*, 721 F.2d 1540, 1553, 220 USPQ 303, 312-13 (Fed. Cir. 1983).

Under 35 U.S.C. §103, in order to set forth a case of prima facie obviousness, the differences between the teachings in the cited reference must be evaluated in terms of the whole invention, and the prior art must provide a teaching or suggestion to the person of ordinary skill in the art to have made the changes that would produce the claimed product. See, *e.g.*, *Lindemann Maschinen-fabrik Gmbh v. American Hoist and Derrick Co.*, 730 F.2d 1452, 1462, 221 U.S.P.Q.2d 481, 488 (Fed. Cir. 1984). The mere fact that prior art may be modified to produce the claimed product does not make the modification obvious unless the prior art suggests the desirability of the modification. *In re Fritch*, 23 U.S.P.Q.2d 1780 (Fed. Cir. 1992); see, also, *In re Papesh*, 315 F.2d 381, 137 U.S.P.Q. 43 (CCPA 1963). In addition, if the proposed modification or combination of the prior art would change the principle of operation of the prior art invention being modified, then the teachings of the references are not sufficient to render the claims prima facie obvious. In re Ratti, 270 F.2d 810, 123 USPQ 349 (CCPA 1959).

The Claims

Claims 1-3, 5-7, 9, 11-14 and 34 are discussed above.

A. THE ANTICIPATION REJECTION

The disclosure of O'Brien *et al.*

O'Brien *et al.* discloses a protein identified therein as TADG-15, which is an MTSP1 variant, with a sequence of amino acids as set forth as SEQ ID NO:2. The reference also

discloses a comparison of the amino acid sequence of the protease domain of TADG-15 (SEQ ID NO:14) with other serine protease catalytic domains (see Figure 2). O'Brien *et al.* discloses that TADG-15 is a highly over-expressed gene in tumors and suggests that TADG-15 is novel in its component structure of domains because it has a protease catalytic domain that could be released and used as a diagnostic and which has the potential for a target for therapeutic intervention (col. 15, lines 31-38). O'Brien *et al.* states that TADG-15 can be expressed in host cells, for example from a construct including SEQ ID NO:1 (the nucleic acid sequence encoding the full-length TADG-15) and/or chemically synthesized. O'Brien *et al.* discloses in Example 7 that quantitative PCR was performed using sense and antisense primers for TADG-15. O'Brien discloses in Example 9 the use of 20mers derived from the catalytic domain of TADG-15 as specific primers and using the specific sequence of the full domain of the catalytic site of TADG-15 as a probe for Northern blot analysis and using the sequence for the TADG-15 catalytic domain of the protease as a probe to screen Hela and ovarian tumor cDNA libraries. O'Brien *et al.* does not disclose, teach or suggest isolation of the protease domain as a single-chain polypeptide.

Analysis

Claims 6, 7, 9 and 14 are cancelled herein without prejudice or disclaimer. Thus, the rejection is moot as applied thereto. O'Brien *et al.* does not anticipate any of the instant claims. As explained above, claim 1 and claims dependent thereon are not directed to a full-length MTSP polypeptide. The claims are directed to a polypeptide that includes an MTSP protease domain or smaller catalytically active portion thereof as the only portion of the polypeptide from an MTSP and the polypeptide does not include any additional MTSP regions. In addition, the claimed polypeptides are single-chain polypeptides. The polypeptides disclosed by O'Brien *et al.* do not possess all of these characteristics.

First, SEQ ID NO:2 disclosed by O'Brien *et al.* is a full-length MTSP. It includes not only a protease domain, but additional MTSP residues, as evidenced by the disclosure shown in Fig. 2 of O'Brien *et al.* SEQ ID NO:2 of O'Brien *et al.* includes a cytoplasmic domain, a transmembrane domain, a CUB repeat, a ligand binding repeat of LDL receptor-like domain in addition to the serine protease domain (see Figure 10). Hence, SEQ ID NO:2 is not a disclosure of an isolated substantially purified polypeptide where a protease domain or a smaller catalytically active portion of the protease domain is the only MTSP portion of the polypeptide. Therefore, the disclosure of SEQ ID NO:2 by O'Brien *et al.* does not anticipate any of the instant claims.

Second, O'Brien *et al.* does not disclose the expression, isolation nor purification of SEQ ID NO:14., which is a subset of the sequence of amino acids set forth as SEQ ID NO:2 in O'Brien *et al.* O'Brien *et al.* states that SEQ ID NO:14 shows the serine protease catalytic domain of TAGD-15. The only mention of SEQ ID NO: 14 in the disclosure of O'Brien *et al.* is in Figure 2 (it is not even described in the sequence listing). Figure 2 shows a sequence comparison of SEQ ID NO:14 with protease domains from other proteases, including hepsin, trypsin, chymotrypsin and tissue plasminogen activator. SEQ ID NO. 14 is a representation; it is not an isolated polypeptide.

Applicant respectfully submits that a comparison of sequences of protease domains is not a disclosure of an isolated, substantially purified single chain polypeptide that includes an MTSP protease domain or smaller catalytically active portion thereof as the only portion of the polypeptide from an MTSP where the polypeptide does not include any additional MTSP regions. The Examiner states that O'Brien *et al.* does not purify the protein identified as SEQ ID NO: 14 (see Office Action, page 20). Further, O'Brien *et al.* does not disclose isolating a protein that has the amino acid sequence as set forth as SEQ ID NO:14. Thus, the disclosure of SEQ ID NO:14 by O'Brien *et al.* does not disclose every element of claim 1 and therefore does not anticipate the claimed subject matter.

Third, O'Brien *et al.* does not disclose a substantially purified single chain polypeptide that includes an MTSP protease domain or smaller catalytically active portion thereof as the only portion of the polypeptide from an MTSP where the polypeptide does not include any additional MTSP regions. The reference does not disclose isolation of a single chain polypeptide that has the amino acid sequence of SEQ ID NO:14. Setting forth the sequence of a domain in the polypeptide is not a disclosure of an isolated polypeptide.

The Examiner's statement that "a single chain polypeptide is one sequence of amino acids beginning with a carboxyl end and terminating with an amino end, where the amino acids are connected via peptide bonds" does not address the element as claimed. The instant claims are directed to an isolated single-chain polypeptide, not a representation thereof. As discussed in the previous Response, and known in the art of serine proteases as evidenced by the art of record, until the disclosure of the instant application, one of skill in the art understood MTSP serine proteases to be active only as *two chain* polypeptides. For example, Lu *et al.* (1999) *J. Biol. Chem.* 272: 31293-300, discloses that as expressed, the MTSP polypeptide is an inactive single-chain zymogen. Cleavage of the single-chain MTSP results in the production of a two-chain polypeptide where the protease domain is covalently bonded

to the upstream polypeptide sequence by a disulfide bond, which results in an active serine protease. Hence, one of ordinary skill in the art, in light of the knowledge of the art, would view O'Brien *et al.* as disclosing a polypeptide sequence of a serine protease zymogen and would expect the protease domain to be part of a two chain polypeptide. One of ordinary skill in the art would not view a sequence ID setting forth a domain without further disclosure as an isolated polypeptide.

To be an anticipatory reference, a reference must put one of ordinary skill in the art in possession of what is claimed. The disclosure of O'Brien *et al.* provides no disclosure of an isolated single chain protease domain.

B. THE OBVIOUSNESS REJECTION

Differences Between the Claims and the Teachings of O'Brien *et al.*

As explained above, O'Brien *et al.* teaches a protein identified therein as TADG-15 with a sequence of amino acids as set forth as SEQ ID NO:2. The reference teaches only the expression of the full-length TADG-15 in host cells. The reference does not provide any teaching or suggestion of any forms of TADG-15 that possess serine protease activity. The reference provides the linear amino acid sequence of SEQ ID NO:14, the stated protease domain of TADG-15, but the reference provides no teaching or suggestion of how one of ordinary skill in the art could generate a single-chain polypeptide containing such sequence and no other MTSP sequence. O'Brien *et al.* does not teach or suggest isolation or purification of a protein having an amino acid sequence set forth as SEQ ID NO:14.

Analysis

It is respectfully submitted that the Examiner has failed to set forth a case of *prima facie* obviousness because of the following:

The teachings of O'Brien *et al.* do not result in the instantly claimed compositions.

As explained above, claim 1 is not directed to the full-length protease. Claim 1 and its dependent claims are directed to polypeptides including a protease domain or a smaller catalytically active portion thereof, where the protease domain or a smaller catalytically active portion thereof is the only part of the polypeptide from an MTSP, where the polypeptide is a single chain and where the protease domain or a smaller catalytically active portion thereof has serine protease activity as a single chain. O'Brien *et al.* fails to teach or suggest polypeptides that include all of these features.

O'Brien *et al.* teaches a full-length TADG-15 polypeptide. TADG-15 shares sequence identity with MTSP1; hence TADG-15 (SEQ ID NO:2 of O'Brien *et al.*) is not a

polypeptide where the protease domain or a smaller portion of the protease domain is the only MTSP portion of the polypeptide. Further, there is no teaching or suggestion of smaller fragments of TADG-15 that are single-chain polypeptides and that retain serine protease activity. The smaller fragments of TADG-15 taught by O'Brien *et al.* are small antigenic fragments, of from 10-50 residues, that have only the property of binding to a TADG-15-specific antibody (see, for example at col.9, lines 22-39). There is no teaching or suggestion that the fragments of TADG-15 retain catalytic activity.

Additionally, although O'Brien *et al.* teaches a linear sequence of amino acids set forth as SEQ ID NO:14 that includes a sequence identified as the protease domain of TADG-15, it does not teach or suggest expressing or isolating a protein with an amino acid sequence as set forth as SEQ ID NO:14. The application does not teach or suggest any expression of SEQ ID NO:14. Nor does it teach or suggest how to make a polypeptide including such as sequence. O'Brien *et al.* suggests that the protease catalytic domain of TADG-15 "could be released" and used as a diagnostic but does not teach or suggest that such a "released" protease domain would be a single-chain form.

Although the Office Action alleges that one of ordinary skill in the art could routinely express heterologous proteins and therefore would have had a reasonable expectation of success to express the protease domain, the art evidences that a single-chained polypeptide would not have been expected to have protease activity. As discussed above, at the time of filing the instant application, one of skill in the art recognized that any active protease domain of an MTSP polypeptide was a two-chain polypeptide (for example, see Lu *et al.* (1999) *J. Biol. Chem.* 272: 31293-300), with the protease domain disulfide bonded to another portion of the MTSP polypeptide. The literature at the time of filing the instant application taught that MTSP serine proteases are synthesized as inactive single-chain zymogens that are activated by cleavage, which forms double-chain polypeptides. This two-chain structure was taught in the art to be critical for serine protease function. Hence, in the absence of the instant application, the art at the time of filing evidenced that single-chain serine protease polypeptides were inactive (zymogens).

In light of the what was known in the art at the time of filing the original application, it would not have been obvious that a single-chain polypeptide with an MTSP serine protease domain or catalytically active portion thereof and no other portion of the MTSP polypeptide would have protease activity. Without further teachings specifically for the generation of a single-chain polypeptide that includes an MTSP protease domain or catalytically active

portion thereof as the only MTSP portion and that possesses serine protease activity as a single chain, O'Brien *et al.* does not teach or suggest the polypeptides of claim 1. Therefore, the Examiner has failed to set forth a *prima facie* case of obviousness.

VIII. THE REJECTION OF CLAIMS 35, 36 AND 40-42 UNDER 35 U.S.C. §103(a)

Claims 35, 36 and 40-42 are rejected under 35 U.S.C. § 103(a) as being unpatentable over O'Brien *et al.* (U.S. Patent No. 5,972,616) because O'Brien *et al.* allegedly teaches a polypeptide identified as SEQ ID NO:2 therein with identity to MTSP1 of the instant application. It is alleged that the reference teaches making fragments of SEQ ID NO:2, linking the fragments to a polypeptide and linking such polypeptides to solid supports.

This rejection is respectfully traversed.

Relevant Law

See above.

The Claims

Claims 35 and 36 are directed to conjugates that include polypeptides of claim 1 and a targeting agent. The conjugates have serine protease activity. Claims 40-42 are directed to solid supports that include two or more polypeptides of claim 1.

Analysis

It is respectfully submitted that the Examiner has failed to set forth a case of *prima facie* obviousness because of the following:

The teachings of O'Brien *et al.* do not result in the instantly claimed compositions.

Claims 35, 36 and 40-42 ultimately depend from claim 1. As explained in detail above, O'Brien *et al.* does not teach or suggest a polypeptide that includes an MTSP protease domain or a smaller catalytically active portion thereof, where the MTSP protease domain or a smaller catalytically active portion thereof is the only part of the polypeptide from an MTSP, where the polypeptide is a single chain and where the MTSP protease domain or a smaller catalytically active portion thereof has serine protease activity as a single chain. Thus, O'Brien *et al.* does not teach or suggest every element of claim 1. Hence, claim 1 is nonobvious over O'Brien *et al.* and therefore claims 35, 36, 40 and 41, which ultimately depend from claim 1, also are nonobvious over O'Brien *et al.*

VIII. REJECTION OF CLAIMS 1, 16, 18-20, 34 AND 137 UNDER 35 U.S.C. §103(a)

Claims 1, 16, 18-20, 34 and 137 are rejected under 35 U.S.C. § 103(a) as being unpatentable over O'Brien *et al.* (U.S. Patent No. 5,972,616) and Estell *et al.* in view of

Takeuchi *et al.* because it is alleged that O'Brien *et al.* teaches a serine protease domain of an MTSP polypeptide but does not teach replacing free Cys residues with Ser residues, but Estell *et al.* in light of Takeuchi *et al.* allegedly cures this defect. The Examiner alleges that it was well known in the art that proteins form disulfide bonds through SH groups of Cys residues. It is alleged that Takeuchi *et al.* teaches that position 731 normally forms a disulfide bond with a Cys residue in the pro-protease domain. The Office Action alleges that Estell *et al.* teaches that Cys residues replaced with Ser residues decrease a polypeptide's susceptibility to oxidation. The Office Action concludes that it would have been obvious to one of ordinary skill in the art to replace a free Cys residue in the protease domain taught by O'Brien *et al.* with a Ser residue in order to enhance stability of the protein. It is alleged that there would have been a reasonable expectation of success because Estell *et al.* teaches that such changes successfully decrease a protein's susceptibility to oxidation.

This rejection is respectfully traversed.

Relevant Law

See related section above.

The Claims

Claim 1 is described above. Claims 16, 18-20, 34 and 137 ultimately depend from claim 1 and are directed to various embodiments thereof. Claim 16 is directed to polypeptides of claim 1 that include as an element replacement of up to about 60% of the amino acids of the protease domain or catalytically active portion thereof replaced with another amino acid. Claim 18 specifies the percentage of retained catalytic activity. Claim 19 is directed to polypeptides of claim 1 where a free Cys in the protease domain is replaced with another amino acid and the resulting polypeptide exhibits proteolytic activity. Claim 20 is directed to polypeptides of claim 1 where a free Cys in the protease domain is replaced with a serine. Claim 34 depends from claim 1 and specifies the MTSP. Claim 137 depends from claim 16 and specifies various substrates.

Differences Between the Claims and the Teachings of the Cited References

O'Brien *et al.* and Takeuchi *et al.*

The teachings of O'Brien *et al.* and Takeuchi *et al.* are discussed above.

Estell *et al.*

Estell *et al.* teaches a method for producing prokaryotic carbonyl hydrolase enzymes, including subtilisin, in recombinant host cells. The method includes introducing mutations into the enzyme sequence including those that exhibit oxidative stability. Amino acids that

can be mutated for oxidative stability according to Estell *et al.* include replacing tryptophan, methionine, cysteine and lysine with an amino acid such as alanine or serine.

Analysis

Claim 34

The rejection as applied to claim 34 appears to be without merit. The Examiner alleges that the combination of O'Brien *et al.* and Estell *et al.* in light of Takeuchi *et al.* teaches replacing free Cys residues in a serine protease domain with Ser residues. Claim 34 depends from claim 1 and recites that the MTSP is selected from among corin, MTSP1, enteropeptidase, human airway trypsin-like protease (HAT), TMPRSS2 and TMPRSS4. Claim 34 is not drawn to a polypeptide that includes free Cys residues substituted with Ser residues or a polypeptide where up to about 60% of the amino acids of the protease domain or catalytically active portion thereof are replaced with another amino acid. The rejection as applied to claim 34 should be withdrawn.

Claims 16, 18-20 and 137

It is respectfully submitted that the Examiner has failed to set forth a case of *prima facie* obviousness. First it is noted that of these claims only claims 19 and 20 remain pending. Claim 19 is directed to a polypeptide of claim 1, where a free Cys in the protease domain is replaced with another amino acid, whereby the resulting polypeptide exhibits proteolytic activity. Claim 20 specifies that the free Cys is replaced by serine.

The combination of teachings of O'Brien *et al.* with the teachings of Estell *et al.*, and Takeuchi *et al.* does not result in the instantly claimed polypeptide

As noted above, if an independent claim is non-obvious, then claims dependent thereon are also nonobvious. Combining the teachings of O'Brien *et al.* with the teachings of Estell *et al.* and Takeuchi *et al.* does not teach or suggest the polypeptides of claim 1, and therefore the combination also does not teach or suggest the polypeptides of claims any of claim 16, 18-20 and 137, which ultimately depend from claim 1.

The Examiner states that O'Brien *et al.* does not teach or suggest a serine protease domain of an MTSP where a free Cys residue is replaced with a Ser residue. In addition, O'Brien *et al.* does not teach or suggest an MTSP protease domain or catalytically active fragment thereof where up to about 60% of the amino acids are replaced with another amino acid. O'Brien *et al.* does not teach or suggest an MTSP protease domain or catalytically active fragment thereof that has a free Cys residue. Further, as explained in detail above, O'Brien *et al.* does not teach or suggest a single chain polypeptide that includes an MTSP protease

domain or smaller portion with catalytic activity as a single chain, where the polypeptide does not include any additional MTSP portions, and the single chain polypeptide has serine protease activity.

Takeuchi *et al.* does not remedy these defects. As discuss above, Takeuchi *et al.* does not teach a single chain polypeptide that includes an MTSP protease domain or smaller portion thereof as the only MTSP portion of the polypeptide where the protease domain or smaller portion thereof has catalytic activity as a single chain. Takeuchi *et al.* teaches a full-length MT-SP1 and a *two*-chain activated polypeptide that includes the protease domain disulfide bonded to the pro-domain. There is no teaching or suggestion by Takeuchi *et al.* to generate a single-chain polypeptide or that the protease domain as a single-chain without its disulfide bonded pro-domain portion would be catalytically active. Further, Takeuchi *et al.* does not teach or suggest an MTSP protease domain having a free Cys residue. As the Examiner points out, Takeuchi *et al.* teaches that the cysteine residue at position 731 of SEQ ID NO:2 forms a disulfide bond with a cysteine residue in the pro-domain (see page 11060 top left paragraph and Figure 4). As shown in Figure 4, Takeuchi *et al.* teaches that *every* cysteine residue of the protein is disulfide bonded. Thus, because all of the cysteine residues of the polypeptide of Takeuchi *et al.* are disulfide bonded, Takeuchi *et al.* does not teach or suggest an MTSP protease domain having a free Cys residue.

Estell *et al.* also fails to remedy the defects of O'Brien *et al.* and Takeuchi *et al.* Estell *et al.* does not teach or suggest any polypeptides that have any MTSP portions. Hence, it does not teach or suggest any of the polypeptides of claim 1. Estell *et al.* does not teach or suggest an MTSP protease domain having a free Cys residue. Thus, although Estell *et al.* teaches that cysteine residues can be replaced in prokaryotic carbonyl hydrolase enzymes, there is no teaching or suggestion of how to arrive at the instantly claimed polypeptides with the particular features of claim 1 or dependent claims 16, 18-20 and 137.

None of O'Brien *et al.*, Takeuchi *et al.* and Estell *et al.*, alone or in any combination, teaches or suggests polypeptides with the features set forth in claim 1: a single chain polypeptide that includes an MTSP protease domain or smaller portion thereof as the only MTSP portion of the polypeptide where the protease domain or smaller portion thereof has catalytic activity as a single chain. In view of the failure of the references, alone or in any combination, to teach or suggest the polypeptides of claim 1, the combination of the references does not teach or suggest the polypeptides of dependent claims 16, 18-20 and 137, which include all of the limitations of claim 1. Thus, the combination of the teachings of

O'Brien *et al.*, Takeuchi *et al.* and Estell *et al.* does not render any of the claimed subject matter obvious. Therefore, the Examiner has failed to set forth a *prima facie* case of obviousness.

* * *

In view of the amendments and remarks herein, reconsideration and allowance of the application are respectfully requested.

Respectfully submitted,

Stephanie Seidman
Reg. No. 33,779

Attorney Docket No. 17106-017001 / 1607
Address all correspondence to:
Stephanie Seidman
Fish & Richardson P.C.
12390 El Camino Real
San Diego, California 92130
Telephone: (858) 678-5070
Facsimile: (202) 626-7796
email: seidman@fr.com